REMARKS

Amendments to the Claims

Claims 1, 8-12, 17-19, and 26-30 are pending. Claims 2-7, 13-15 and 20-25 have been previously withdrawn without prejudice as drawn to a non-elected invention. Claims 16 and 29 were previously canceled without prejudice or disclaimer. Claims 12, and 17-19 are canceled without prejudice with this amendment. Claims 1 and 8 have been amended.

Claim 1 has been amended to clarify that the second assay system comprises cultured cells and an assay selected from a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay. Support for the amendment is found throughout the specification and at, for example, pages 23-26 and 40-41.

Claim 8 has been amended to clarify that the first assay system includes an expression assay comprising SEQ ID NO: 5 and the candidate test agent is a nucleic acid modulator that modulates the expression of SEQ ID NO: 5. Support for the amendment is found throughout the specification at, for example, page 30.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. Support for the claim amendments are found throughout the specification. No new matter has been added by way of these amendments.

35 USC 102(b) Rejections

Claims 1, 8-9, 11-12, 17-19, and 26-29 were rejected under 35 USC 102(b) as being anticipated by US 2002/00257931 A1 ("Meyers"). Applicants respectfully traverse the rejections.

The Office asserted that Meyers teaches the claimed invention because it teaches a screening method for identifying a compound that binds to or modulates the activity of an SNF1LK protein and also teaches screening assays for identifying modulators (i. e., candidate or test compounds or agents) which have a stimulatory or inhibitory effect on the expression or activity of

SNF1LK (citing paragraphs [0298 – 0301]). The Office stated that any agent that has an effect on SNF1LK is considered a candidate PTEN pathway modulating agent because these proteins are in the same pathway. Based on this teaching (and apparently the teaching in the instant specification relating to the PTEN pathway), the Office concluded that Meyers teaches a method for identifying a candidate PTEN pathway modulating agent comprising the first assay system steps recited in the instantly claimed methods.

With respect to measuring a change in the PTEN pathway (steps (d) –(f) of the instantly claimed methods), the Office asserted that paragraph [0220] of Meyers teaches that a mutant SNF1LK can be assayed for the ability to: 1) regulate transmission of signals from cellular receptors; 2) control entry of cells into mitosis; 3) modulate cellular differentiation; 4) modulate cell death; or 5) regulate cytoskeleton function, all of which allegedly can be considered in the PTEN pathway.

Furthermore, the Office also asserted that paragraph [0308] of Meyers teaches how to determine the ability of the SNF1LK protein to bind to or interact with a SNF1LK target molecule by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+}, diacylglycerol, IP3, etc.) detecting catalytic/enzymatic activity of the target (an appropriate substrate), detecting the induction of a reporter gene, or detecting a target-regulated cellular response. The Office stated that since no specific steps in the second assay system are recited in the instant claims other than a general cell based assay, it includes the assays taught by Meyers in paragraphs [0220] and [0308] and therefore Meyers teaches the claimed methods.

Under 35 U.S.C. § 102(b), a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987). No difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881

(S.D. Ind.1993); Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed.Cir.1988) ("For a prior art reference to anticipate in terms of 35 U.S.C. Sec. 102, every element of the claimed invention must be identically shown in a single reference."). All elements of the claimed invention must be contained in a single prior art disclosure and must be arranged in the prior art disclosure as in the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984); *In re Bond*, 910 F.2d 831, (Fed. Cir.1990) (the elements must be arranged as required by the claim); Lindemann *Maschinenfabrik v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed.Cir.1984) (the elements must be arranged as in the claim under review). Furthermore, the identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

Moreover, to serve as an anticipatory reference, the prior art reference must provide an enabling disclosure of the claimed subject matter. *In re Hoeksema*, 399 F.2d 269 (CCPA 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention' 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'… ."). Thus, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000); *In re Donohoe*, 766 F.2d 531, 533 (Fed Cir. 1985); M.P.E.P. §2121.01. The mere naming or description of the subject matter is not considered an enabling disclosure if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003); *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962).

A reference is considered enabling if it describes the subject matter of the claimed invention sufficiently to have placed it in possession of the public. *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000); *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); M.P.E.P. §2121.01. To place the invention in the

possession of the public, the reference must be "so precise and so particular that any person skilled in the art to which the invention belongs can construct and operate it without further experiments and without further exercise of inventive skill." *In re LeGrice*, 301 F.2d 929, 934 (CCPA 1962) (quoting I Robinson on Patents, Sec. 325 (1890)); *In re Brown*, 141 USPQ 245, (CCPA 1964).

The present invention is directed to methods of identifying a candidate PTEN pathway modulating agent. Using a *C. Elegans* genetic screen specifically designed to identify modifiers of the PTEN pathway, Applicants were the first ones to determine that SNF1LK is involved in the PTEN pathway. Based on this finding, the present claims are directed to a method of identifying a candidate PTEN pathway modulating agent using a first assay system capable of detecting the expression of a specified SNF1LK nucleic acid and a second assay system capable of measuring a change in the PTEN pathway.

Therefore, to anticipate the claims, Meyers must provide an enabling disclosure for a method of identifying a candidate PTEN pathway modulating agent comprising the steps of: (a) providing a first assay system comprising SEQ ID NO: 5 or a functionally active fragment thereof, wherein the assay system is capable of detecting the expression of SEQ ID NO: 5; (b) contacting the first assay system with a test agent that modulates SEQ ID NO: 5; (c) determining a difference in the expression of SEQ ID NO: 5 in the presence or absence of the test agent, wherein a difference in the expression of SEQ ID NO: 5 identifies the test agent as a candidate PTEN pathway modulating agent; (d) confirming that the test agent of (b) is a candidate PTEN pathway modulating agent by providing a second assay system that measures a change in the PTEN pathway, wherein the assay is selected from a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay; (e) contacting the second assay system with the test agent of (b); and (f) determining a change in the PTEN pathway in the second assay system, wherein a change in the PTEN pathway between the presence and absence of said test agent confirms the test agent as a candidate PTEN pathway modulating agent. Each and every step (a) – (f) must be described in as complete detail as is contained in the instant claims and must be arranged in the prior art disclosure

as in the claimed methods..

Applicants submit that Meyers fails to anticipate the instant invention because it fails to teach each and every step in as much detail and as arranged in steps (a)-(f) of the claimed screening assay methods. Specifically, Meyers fails to teach steps (d) – (f). Despite the fact that Meyers fails to mention the PTEN pathway or even contemplate an association between SNF1LK and the PTEN pathway, the Office asserted that the second assay system recited in the instant claims (steps (d) – (f)) is taught in paragraph [0220] of Meyers, which is reproduced in its entirety here:

> In a preferred embodiment, a mutant 3714, 16742, 23546, or 13887 protein can be assayed for the ability to: 1) regulate transmission of signals from cellular receptors, e.g., cardiac cell growth factor receptors; 2) control entry of cells into mitosis; 3) modulate cellular differentiation; 4) modulate cell death; or 5) regulate cytoskeleton function, e.g., actin bundling.

However, a review of the Meyers reference reveals that paragraph [0220] is found in Section I of the application entitled "Isolated Nucleic Acid Molecules" (paragraphs [0197] – [0230]) and not in the section of the application pertaining to screening assays methods (screening assays are described in Section V. A. of the application, i.e., paragraphs [0299] – [0319]). Section I of the application describes various characteristics of the polynucleotides of interest, including the structures of fragments, naturally-occurring variants, homologues, and various mutants created by mutagenesis. Thus, it is only in the context of describing the structural characteristics of various SNF1LK nucleic acid molecules, and not in the context of screening a test agent in screening assay methods, that Meyers suggests designing a mutant SNF1LK to determine whether the mutated version can modulate various cellular pathways (presumably to determine the function of SNF1LK).

Applicants submit that it is improper to isolate and juxtapose a teaching concerning unrelated subject matter (the structure of mutant SNF1LK molecules) with a description of screening assays and conclude that Meyers teaches the instantly claimed screening assay methods. The teaching in paragraph [0220] is spatially and conceptually divorced from the description of screening assay

methods subsequently found in paragraphs [0299] – [0319] of Meyers. Thus, it is clear that Meyers did not contemplate, much less teach or suggest, modifying the described screening assays methods to further include the steps of assaying a mutant SNF1LK for the ability to regulate the recited cellular pathways. The improper juxtaposition of unrelated subject matter violates the rule of anticipation that the steps of the claimed method must be arranged in the prior art disclosure as in the claimed method.

Furthermore, even if, for the sake of argument, the combination of unrelated teachings was proper, it still does not anticipate the present invention. Steps (d) - (f) of the claimed methods require contacting a second assay system that measures a change in the PTEN pathway with the test agent used in previous steps and determining a change in the PTEN pathway in the presence of the test agent. None of the steps of the claimed assay employ the use of a mutant SNF1LK as taught by Meyers. Furthermore, Meyers fails to mention the PTEN pathway or an association between SNF1LK and the PTEN pathway and also fails to mention the specific assays recited in step (d). Meyers only suggests assaying a mutant SNF1LK for the ability to regulate some general cellular pathways, but fails to provide further details as to which specific pathway(s), out of the numerous various pathways, may be involved in such regulation. Thus, the teachings in Meyers cited by the Office fail to teach each and every step of the claimed screening assay in as complete detail as is contained in the instant claims.

The Office also asserted that steps (d) – (f) of the instantly claimed methods are taught in paragraph [0308] of Meyers, which teaches how to determine the ability of the SNF1LK protein to bind to or interact with a SNF1LK target molecule by determining the activity of the target molecule (e.g., detecting induction of second messengers, such as intracellular Ca2+, diacylglycerol, and IP3, detecting catalytic/enzymatic activity of the target, detecting induction of a reporter gene, or detecting a target-regulated cellular response). The Office stated that since no specific steps in the second assay system are recited in the instant claims other than a general cell based assay, it includes the assays taught by Meyers in paragraphs [0220] and [0308].

Section V. A., paragraphs [0299] – [0319], in Meyers relates to screening assays. The first paragraph [0300] states that the invention provides a method (screening assay) for identifying modulators (i.e., test agents) which bind to SNF1LK proteins, have a stimulatory or inhibitory effect on SNF1LK expression or activity, **or** have a stimulatory or inhibitory effect on the expression or activity of a SNF1LK substrate. It is clear from this description that the section on screening assays intends to describe separate screening assay methods for (1) identifying test agents that bind to SNF1LK proteins, (2) identifying test agents that have a stimulatory or inhibitory effect on SNF1LK expression or activity, and (3) identifying test agents that have a stimulatory or inhibitory effect on the expression or activity of a SNF1LK substrate.

Paragraphs [0301] – [0303] teach, in one embodiment, a method for screening test compounds which are substrates of SNF1LK protein and, in another embodiment, a method for screening test compounds which bind to or modulate the activity of SNF1LK protein, including the ability of SNF1LK to interact with its cognate ligand. Paragraph [0316] teaches a method for screening test compounds that stimulate or inhibit SNF1LK mRNA or protein expression. Paragraphs [0304] – [0308] teach cell-based assays comprising contacting a cell expressing a SNF1LK target molecule with a test compound and determining the ability of the test compound to modulate the activity of the SNF1LK target molecule, including the ability of SNF1LK to bind to or phosphorylate the target molecule; paragraphs [0309] – [0313] relate to various cell-free assays; paragraphs [0314] –[0315] describe methods for immobilizing SNF1LK proteins; paragraphs [0317]- [0318] describe specific two-hybrid assays; and paragraph [0319] relates to novel agents identified by the screening assays.

It is clear from reading the Meyers reference that the assays described above are separate assay methods, i.e., there is no indication whatsoever that the various assays should be combined or performed together. For example, the assays described in paragraphs [0301] – [0303] (method for screening a test compound that modulates the activity of SNF1LK) are separate and intended to be distinct from the assays described in paragraphs [0304] – [0308] (method for screening a test compound that modulates the activity of a SNF1LK target

molecule). This is evidenced by the fact that paragraph [0301] starts with "[I]n one embodiment, the invention provides…" and paragraph [0304] starts with "[I]n another embodiment, an assay is a cell-based assay comprising…" (which language indicates a separate assay), as opposed to starting with "[I]n one embodiment, the assay further comprises…" (which language indicates the same screening assay has additional steps). Therefore, Applicants submit that Meyers fails to anticipate the instant claims because it fails to teach a screening assay having each and every step (a) – (f) of the claimed screening assay methods.

Even if, for the sake of argument, the assays of paragraphs [0301] – [0303] and paragraph [0316] could be properly combined with the assay(s) of paragraph [0308], the combination still would not anticipate the claimed methods. As indicated above, paragraphs [0301] – [0303] and [0316] teach a method for screening test compounds which modulate the expression or activity of SNF1LK and paragraph [0308] teaches a method for determining the ability of a test compound to modulate the activity of an SNF1LK target molecule, for example, by detecting a target-related cellular response. However, other than indicating that SNF1LK has kinase activity, Meyers fails to teach or suggest a target-related cellular response for SNF1LK, and certainly fails to teach using a second assay system to measure a change in the PTEN pathway. Thus, the teachings in Meyers cited by the Office fail to teach each and every step of the claimed screening assay in as complete detail as is contained in the instant claims. Moreover, Meyer does not suffice as prior art because it fails to provide an enabling disclosure for each and every step (a) – (f) of the claimed assay. Specifically, given that Meyers et al. does not contemplate identifying a candidate PTEN pathway modulating agent , it fails to teach steps (d)- (f) of the claimed methods. The mere teaching to "detect a target-related cellular response" does not amount to a teaching of using a second assay system to measure a change in the PTEN pathway, much less amount to an enabling disclosure or a detailed description of such an assay system.

Although Applicants disagree with the Office's assertions for the reasons provided here, solely to advance prosecution, claim 1 has been amended to recite that the assay measuring a change in the PTEN pathway is selected from

a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay, none of which assays are taught or suggested in Meyers.

For the reasons set forth above, Meyers fails to teach each and every step of the claimed methods and therefore fails to anticipate the present invention. Accordingly, Applicant respectfully request withdrawal of the 35 USC 102 rejections.

35 USC 103(a) Rejections

Claim 10 was rejected under 35 USC 103(a) as allegedly being unpatentable over Meyers et al. in view of Summerton et al., (Biochimica et Biophysica Acta 1489: 141-158 (1999)) or Stein et al. (Antisense & Nucleic Acid Drug Dev., 7:151-157 (1997)). Applicants respectfully traverse the rejection.

The Office relied on the teachings of Meyer et al. as described above and stated that Summerton et al. and Stein et al. teach the advantages of using a PMO as an antisense oligomer. The Office alleged that it would have been obvious to use PMOs in the claimed methods to avoid the known problems associated with antisense technology and that one of ordinary skill in the art would have had a reasonable expectation of success because the art teaches that RNase-dependent and RNase-independent oligos (ie PMOs) can be used interchangeably.

The Office specifically argued that regardless of the stated purpose in the preamble, the first assay measures the effect of an agent on SNF1LK, which effect is evaluated in the method of identifying an agent that modulates the PTEN pathway. The Office concluded that the method of identifying a PTEN pathway modulating agent through the effect of the agent on the expression level of the SNF1LK is within the limitation of the teachings of Meyers since Meyers teaches various cell based assays as the second assay (i.e., presumable as discussed in paragraphs [0220] and [0308]).

Contrary to the Office's allegations, the teachings of Meyers, Summerton and Stein, alone or in combination, do not render obvious the present invention. To meet the requirements for a *prima facie* case of obviousness, the Office must demonstrate that the references teach or suggest <u>all</u> the limitations of the

claims. Post-KSR, the Board of Patent Appeals and Interferences (BPAI) has continued to maintain that:

> [A]n examiner must make "a searching comparison of the claimed invention — *including all its limitations* - with the teaching of the prior art." *In re Ochiai,* 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.,* 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka,* 490 F.2d 981, 985 (CCPA 1974)). *Ex Parte* Wada, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished). *See also, Ex parte* Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished).

Thus, the combined teachings of Meyers, Summerton and Stein must teach a screening assay comprising the steps of (a) – (f), which includes contacting a second assay system that measures a change in the PTEN pathway with the test agent and determining a change in the PTEN pathway in the presence of the test agent, wherein the assay in the second assay system is selected from a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay.

Applicants submit that Meyer, Summerton and Stein, alone or in combination, fail to teach or suggest a method for identifying a candidate PTEN modulating agent using a first assay system capable of detecting the expression of SEQ ID NO: 5 comprising steps (a) – (c) and a second assay system capable of measuring a change in the PTEN pathway comprising steps (d) – (f).

First, for all of the reasons set forth above, Meyers fails to teach or suggest all of the limitations of the claim. Specifically, Meyers fails to teach steps (d)- (f) of the claimed methods, as previously explained. Further, neither Summerton nor Stein cure the deficiencies of Meyers. Neither Summerton nor Stein are concerned with SNF1LK or the PTEN pathway and therefore offer no teaching whatsoever in this regard. Thus, Summerton and Stein fails to teach any of steps of the claimed screening assay methods and therefore fails to supplement the teachings of Meyers so as to arrive at the presently claimed methods of identifying a candidate PTEN modulating agent employing the steps of (a) – (f). Thus, the combined teachings of Meyer, Summerton, and Stein fail to teach or suggest all of the limitations of the presently claimed methods, and thus

fail to render the instant invention obvious.

Furthermore, one skilled in the art would not have been motivated to modify the combined teachings of Meyer, Summerton and Stein to arrive at the presently claimed methods. None of these references even mention the PTEN pathway. Thus, they fail to recognize any association between SNF1LK and the PTEN pathway and certainly fail to suggest with any reasonable expectation of success that an SNF1LK polynucleotide or a test agent that modulates SNF1LK could be used in an assay to identify a PTEN pathway modulating agent. Accordingly, they fail to suggest that one should further test the SNF1LK-modulating agent in a second assay system capable of measuring a change in the PTEN pathway comprising steps (d) – (f), and, in particular, they fail to teach a second assay system in which the assay is selected from a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay.

Applicants respectfully submit that the Office has failed to establish a prima facie case of obviousness for the reasons set forth above. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on the teachings of Meyer, Summerton and Stein.

Claims 8, 9, and 30 were rejected under 35 USC 103(a) as allegedly being unpatentable over Meyers et al. in view of Martinez et al., (PNAS, 99: 14849-14854 (2002)). Applicants respectfully traverse the rejections.

The Office applied the teachings described above to Meyers acknowledging that Meyers does not teach using an siRNA or dsRNA to modulate transcription. However, the Office relied on Martinez et al for teaching the use of siRNA to suppress the expression of mRNA targets. The Office alleged that it would have been obvious to design an siRNA to modulate the polynucleotide sequence of SEQ ID NO: 1 described in Meyer et al. (considered by the Office as a functional equivalent of SEQ ID NO: 5).

Meyers fails to teach or suggest the claimed methods for the reasons previously discussed. Applicants submit that Martinez et al. fails to cure the deficiencies of the teachings of Meyers. Martinez et al. makes no mention of

SNF1LK or the PTEN pathway and therefore offers no teaching whatsoever in this regard. Thus, Martinez et al. fails to supplement the teachings of Meyers and also fails to provide a motivation to supplement the teachings of Meyers so as to arrive at the presently claimed methods of identifying a candidate PTEN pathway modulating agent, in particular a method comprising further testing of an SNF1LK-modulating agent in a second assay system capable of measuring a change in the PTEN pathway comprising steps (d) – (f), in which the assay is selected from a BRDU assay, cell viability assay, tritiated thymidine assay, nucleosome ELISA apoptosis assay, and FOXO nuclear translocation assay.

The combined teachings of Meyers and Martinez et al. fail to teach or suggest all of the limitations of the presently claimed cells, and thus fail to render the instant invention obvious.

Applicants respectfully submit that the Office has failed to establish a prima facie case of obviousness for the reasons set forth above. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection based on the teachings of Meyers and Martinez et al.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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